

Predictors of Cardiovascular Outcomes in Patients with Hypertension and Left Ventricular Hypertrophy

Emphasis on Isolated Systolic Hypertension and Pulse Pressure

Thesis

Anne Cecilie K. Larstorp, M.D.

Section for Cardiovascular and Renal Research

Department of Cardiology

Oslo University Hospital Ullevål

Oslo, Norway

&

Institute of Clinical Medicine,

Faculty of Medicine,

University of Oslo,

Oslo, Norway

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Anne Cecilie K. Larstorp

List of papers

- I. Larstorp ACK, Okin PM, Devereux RB, Olsen MH, Ibsen H, Dahlöf B, Kjeldsen SE, Wachtell K.
Changes in electrocardiographic left ventricular hypertrophy and risk of major cardiovascular events in isolated systolic hypertension: The LIFE study.
J Hum Hypertens 2011;25:178-185.

- II. Larstorp ACK, Okin PM, Devereux RB, Olsen MH, Ibsen H, Dahlöf B, Kjeldsen SE, Wachtell K.
Regression of ECG-LVH is associated with lower risk of new-onset heart failure and mortality in patients with isolated systolic hypertension. The LIFE Study.
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- III. Larstorp ACK, Ariansen I, Gjesdal K, Olsen MH, Ibsen H, Devereux RB, Okin PM, Dahlöf B, Kjeldsen SE, Wachtell K.
Association of pulse pressure with new-onset atrial fibrillation in patients with hypertension and left ventricular hypertrophy: The LIFE study.
Hypertension 2012 – published online ahead of print.

The papers are referred to by their Roman numerals throughout the thesis.

Abbreviations

ACE	Angiotensin-converting enzyme
AF	Atrial fibrillation
ARB	Angiotensin II-receptor blocker
BP	Blood pressure
Bpm	Beats per minute
CCB	Calcium channel blocker
CI	Confidence interval
DBP	Diastolic blood pressure
ECG	Electrocardiogram
ECG-LVH	Electrocardiographic left ventricular hypertrophy
FDA	U.S. Food and Drug Administration
HF	Heart failure
HR	Hazard ratio
ISH	Isolated systolic hypertension
LIFE	Losartan intervention for endpoint reduction in hypertension study
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
MAP	Mean arterial pressure
MI	Myocardial infarction
Non-ISH	Systolic-diastolic hypertension or isolated diastolic hypertension
PP	Pulse pressure
SBP	Systolic blood pressure
SD	Standard deviation
SHEP	The systolic hypertension in the elderly program
Syst-China	The systolic hypertension in China trial
Syst-Eur	The systolic hypertension in Europe trial
UACR	Urine albumin-creatinine ratio
USA	United States of America

Introduction

The Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study is a large randomized, comparative, antihypertensive treatment trial in patients with hypertension *and* ECG-LVH. The database includes standardized, detailed analyses of >100 000 12-lead ECGs taken during the course of the study. Though the study was not primarily designed to address this issue, prespecified secondary analyses provided a unique opportunity to study the effects of ECG-LVH regression on cardiovascular outcomes in a group of hypertensive patients with especially high risk, namely the isolated systolic hypertension (ISH) subgroup. Defined here as having SBP ≥ 160 mm Hg and DBP < 90 mm Hg¹⁻³, these patients all had high pulse pressure (PP) (mean 92 mm Hg at baseline), a marker of arterial stiffness, which has been associated with increased risk of developing atrial fibrillation (AF). Thorough analyses of these issues could provide insight into possible treatment goals in the prevention of cardiovascular morbidity and mortality in these high-risk patients, beyond that of lowering BP, and perhaps, further insight into development of atrial fibrillation in hypertension.

Isolated systolic hypertension

ISH is the most common form of hypertension in the elderly >60 years, accounting for 60-75% of cases^{4,5}, and is a major cardiovascular risk factor⁶⁻⁹.

The pathogenesis of ISH is not completely understood, but mechanisms are most likely age-associated and potentially associated with lifestyle¹⁰. Evidence suggests that increased arterial vascular stiffness (in particular in large arteries)¹¹, increased arterial pulse wave velocity (PWV) and early wave reflection¹², as well as dysregulation of the autonomic nervous system and the renin-angiotensin-aldosterone system (RAAS)^{10,13}, progressive renal dysfunction¹⁴ and increase in salt sensitivity¹⁵, are important factors. Secondary causes of hypertension more rarely lead to ISH^{10,16}.

Placebo-controlled outcome trials (The Systolic Hypertension in the Elderly Program [SHEP]¹⁷, The Systolic Hypertension in Europe Trial [Syst-Eur]¹⁸ and The Systolic Hypertension in China Trial [Syst-China]¹⁹) have demonstrated that antihypertensive treatment of ISH is efficacious; cardiovascular morbidity and mortality was decreased by 30-40% in patients who received antihypertensive therapy compared with placebo. Furthermore, all-cause mortality was reduced by 39% in the Syst-China trial¹⁹, but was

unaffected in the SHEP¹⁷ and Syst-Eur¹⁸ trials. The first comparative drug trial to report cardiovascular outcomes in ISH with ECG-LVH was a LIFE substudy²⁰, demonstrating significantly lower rates of stroke and cardiovascular death in patients randomized to losartan- versus atenolol-based antihypertensive treatment.

Left ventricular hypertrophy

Left ventricular hypertrophy (LVH) is defined as an increase in the mass of the left ventricle. Hypertension causes increased afterload and left ventricular wall stress, which again leads to myocardial hypertrophy (increase in the number and/or size of sarcomeres within each myocardial cell). The prevalence of LVH in patients with hypertension depends on age, severity of hypertension and the method of detection; even in mild or moderate hypertension the prevalence may be as high as 20-50%²¹⁻²⁴.

LVH detected by 12-lead electrocardiogram (ECG)²⁵⁻²⁸ and by echocardiography²⁹⁻³⁵ are common manifestations of preclinical cardiovascular disease that strongly predict cardiovascular morbidity and mortality. Several studies suggest that the increased cardiovascular risk associated with LVH is partly due to myocardial ischemia³⁶⁻³⁸.

ECG-LVH can be measured by several methods; the most commonly used are, perhaps, Sokolow-Lyon voltage³⁹ ($S_{V1} + R_{V5/6}$) and Cornell voltage-duration product^{40,41} (QRS duration \times the Cornell voltage combination [$R_{aVL} + S_{V3}$, with 6 mm added in women]). The threshold values for ECG-LVH are 38 mm for Sokolow-Lyon voltage and 2440 mm \times ms for Cornell voltage-duration product.

Antihypertensive therapy targeted at lowering BP can produce regression of LVH^{26;34;42-47} and reduce, but do not entirely eliminate the increased risk of major cardiovascular events⁴⁸⁻⁵².

Atrial fibrillation and pulse pressure

AF is diagnosed by ECG and defined as a cardiac arrhythmia with: irregular RR intervals, i.e. RR intervals that do not follow a repetitive pattern; no distinct P waves; and usually a variable atrial cycle length, i.e. the interval between two atrial activations, <200 ms (>300 atrial bpm)⁵³.

The prevalence of AF increases with age and underlying heart disease⁵⁴⁻⁵⁷, and the total number of AF patients is increasing⁵⁸. The lifetime risk for the development of AF was $\sim 25\%$ in the Framingham Heart Study⁵⁹. AF is associated with a 4 to 5 fold increased risk of ischemic stroke^{60,61} and with a near doubled risk of cardiovascular death⁶². Hypertension is currently the

most prevalent, potentially modifiable risk factor, accounting for ~14% to 22% of AF cases⁶³⁻⁶⁶.

Increased PP, defined as the difference between SBP and DBP, is a marker of arterial stiffness^{67;68}. Studies have found brachial PP to be an independent predictor of new-onset AF in both general⁶⁹ and hypertensive⁷⁰ populations. Furthermore, brachial PP is a predictor of cardiovascular morbidity and mortality⁷¹⁻⁷⁷ (also in the LIFE study⁷⁸) and its predictive effect increases with age^{74;75;77}.

Aims of the thesis

The aims of the thesis were, first, to investigate the effects of reducing ECG-LVH for cardiovascular morbidity and mortality in patients with ISH and ECG-LVH, and second, to investigate the relation between PP and new-onset AF in patients with hypertension and ECG-LVH. The main hypotheses addressed were:

- Lower in-treatment ECG-LVH is associated with lower risk of stroke, myocardial infarction and cardiovascular death in patients with ISH, and this effect is stronger in patients with ISH than in patients with systolic-diastolic hypertension or isolated diastolic hypertension. (Paper I)
- Lower in-treatment ECG-LVH is associated with lower risk of new-onset HF and total mortality in patients with ISH, and this effect is stronger in patients with ISH than in patients with systolic-diastolic hypertension or isolated diastolic hypertension. (Paper II)
- Higher baseline and in-treatment brachial PP is associated with higher risk of new-onset AF in hypertensive patients with ECG-LVH, and PP is a stronger predictor of new-onset AF than other single BP components like SBP, DBP and MAP. (Paper III)

Materials and methods

Study design and population

The LIFE study is an investigator-initiated, prospective, multicenter, double-blinded, randomized, active-controlled, parallel-group trial⁷⁹⁻⁸¹. The study was designed for comparing the long-term effects of losartan- vs. atenolol-based antihypertensive treatment on the primary composite endpoint of cardiovascular death, MI and stroke in patients with hypertension and ECG-LVH. Other outcome measures were the components of the primary composite endpoint (cardiovascular death, MI and stroke), total mortality, angina pectoris or heart failure requiring admission to hospital, coronary or peripheral revascularization procedures, resuscitated cardiac arrest, new-onset diabetes mellitus and new-onset atrial fibrillation.

The study enrolled 9193 patients aged 55-80 years with previously treated or untreated essential hypertension (mean sitting BP in the range of 160 to 200 mm Hg systolic, 95 to 115 mm Hg diastolic, or both, after one to two weeks of single-blind placebo treatment) having ECG-LVH determined by Cornell voltage-duration product^{40,41} and/or Sokolow-Lyon voltage criteria³⁹ on a screening ECG. Patients were enrolled from June 1995 to May 1997, in Norway, Sweden, Denmark, Finland, Iceland, USA and UK. Exclusion criteria were secondary hypertension; MI or stroke within the previous six months; angina pectoris requiring treatment with β -blockers or CCBs; heart failure or LVEF $\leq 40\%$; or a disorder that, in the treating physician's opinion, required treatment with an ARB, β -blocker, hydrochlorothiazide, or ACE-inhibitor. Patients were followed for 4 or more years with regular visits by 944 local investigators. The investigators followed a treatment schedule; with upward titration of medication targeting a BP of 140/90 mm Hg or lower⁷⁹. The study was endpoint driven, follow-up was ended in September 2001 and the database was locked in December 2001.

In the detailed LIFE data analysis plan that was submitted to the FDA in the USA before unblinding of the study, patients with ISH were prespecified as a subgroup of special interest²⁰. ISH was defined as SBP ≥ 160 mm Hg and DBP < 90 mm Hg after 1 to 2 weeks of receiving placebo. A total of 1320 ISH patients (14.4% of the LIFE population), averaging 70.3 years, were included in the analyses when we investigated the possible effects of regression of ECG-LVH for the risks of the composite endpoint of cardiovascular death, MI

and stroke as well as the components of this endpoint (Paper I). We also performed a comparison of these results with those of the non-ISH patients ($n=7873$).

When we investigated the possible effects of regression of ECG-LVH for the risks of new-onset HF and the combined endpoint of new-onset HF and all-cause mortality, we excluded patients with a history of HF ($n=166$) and thus 1280 ISH patients and 7747 non-ISH patients were eligible for data analyses (Paper II).

We wished to examine whether pulse pressure was a predictor of new-onset AF in this study with 9193 patients with hypertension and ECG-LVH, and if PP was a stronger predictor than other BP components (Paper III). A total of 362 patients with a history of AF and/or AF on their baseline ECG and 21 patients with missing baseline PP were excluded and, thus, 8810 patients with neither a history of AF or AF on their baseline ECG were included in the analyses.

Ethics

The trial protocol was approved by all ethics committees concerned; was in accordance with the Declaration of Helsinki and was overseen by an independent data and safety monitoring board⁷⁹. All participants gave written informed consent. The investigators have the locked database in their position and the exclusive rights to analyze and publish.

Procedures

Brachial blood pressure was measured 24 hours after drug dose (range 22-26 hours) as the average of two recordings with a one-minute interval after patients had been seated for five minutes with the arm positioned so that the location of the stethoscope head was at the level of the heart. Investigators were instructed to use a validated, calibrated manual sphygmomanometer maintained in good condition and a cuff of proper size. In addition, one-minute standing BP was measured before upward titration of study drug; if orthostatic effect was observed, the investigator may have decided not to titrate to the next level⁸².

Electrocardiograms were obtained at study baseline, at 6 months, and at yearly follow-up intervals until study termination or patient death. All ECGs were read by experienced readers blinded to clinical information at the ECG core center at Clinical Experimental Research Laboratory, Department of Medicine, Sahlgrenska University Hospital/Östra, Göteborg, Sweden, under the leadership of Sverker Jern. QRS duration was measured to the nearest 4 ms and the QRS amplitudes to the nearest 0.5 mm (0.05 mV). The product of QRS

duration \times the Cornell voltage combination ($R_{aVL} + S_{V3}$, with 8 mm added in women^{40;41}) was used with a threshold value of 2440 mm \times ms to identify LVH. The sex adjustment of Cornell voltage was reduced from 8 to 6 mm and Sokolow-Lyon voltage ($S_{V1} + R_{V5/6}$) greater than 38 mm was accepted for electrocardiographic eligibility in patients recruited after April 30, 1996 ($n=7708$ in the LIFE study, including 1003 ISH patients)^{80;83}.

Laboratory tests were carried out at two central laboratories that assured comparability of measurements by cross-validation. The Framingham Risk Score was estimated from age, sex, SBP, total and high density lipoprotein cholesterol, smoking status, glucose/diabetes mellitus, and LVH⁸⁴.

Study endpoints

All endpoints were reported by investigators and the source data was verified by independent monitors. An endpoint classification committee of two masked clinicians (Daniel Levy, USA and Kristian Thygesen, Denmark) reviewed clinical records of all reported cardiovascular events to determine whether they met endpoint criteria⁸¹. The committee used results from Minnesota coding of ECGs at the core laboratory for signs of MI or other disorders, however, they were blinded to study ECG-LVH findings when classifying possible morbid or mortal events. Deaths were reported directly to the independent data and safety monitoring board for validation⁸¹. Adverse experiences were monitored and classified as drug related or non-drug related and serious or non-serious.

We aimed to investigate the effect of regression of ECG-LVH on the primary composite endpoint of cardiovascular death, non-fatal MI and non-fatal stroke in ISH patients (Paper I). Furthermore, we wanted to evaluate the effect on the individual endpoints of cardiovascular death, fatal and non-fatal MI and fatal and non-fatal stroke (counting the first occurrence of each component of the primary composite endpoint, whether or not preceded by another component of the primary composite endpoint⁸⁵).

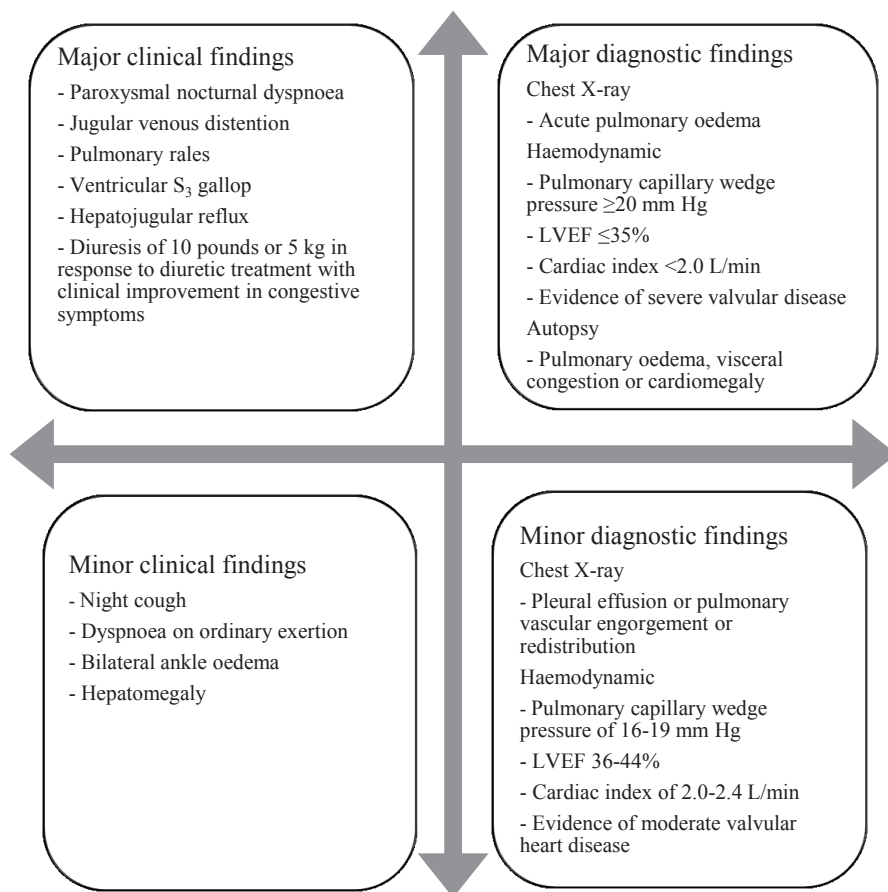
Hospitalization for new-onset HF (Paper II) was based on the HF criteria from the Framingham Heart Study^{86;87} (Figure 1). Furthermore, a composite endpoint of new-onset HF or all-cause death (time to first event) was assessed for several reasons. First, death is a competing event and when comparing ISH to non-ISH it is essential to use the composite because of significant difference in mortality. Second, both incident HF and death were pre-specified endpoints and combining them would increase the number of endpoints and the statistical power. Third, hypertension with LVH may be the most important source of HF

with subsequent high mortality^{26;88-101}. Fourth, this composite has been the primary or secondary endpoint in many outcome trials in patients with HF¹⁰²⁻¹⁰⁵.

New-onset AF was identified by Minnesota coding of annual in-study ECGs at the core laboratory^{79;85} (Paper III). New-onset AF was also reported as an adverse experience by study investigators, however, in our analyses we used a conservative approach and included only the ECG documented endpoints. Care of the patients with new-onset AF was left to the discretion of local investigators.

Figure 1. Hospitalization for new-onset heart failure criteria⁸⁷

(Modified from Supplementary online figure, Paper II)



A definite diagnosis required a minimum of one major clinical plus one major diagnostic finding; or one major clinical plus two minor diagnostic findings; or one minor clinical plus two major or minor diagnostic findings. Minor criteria were only accepted if they could not be attributed to another disease process. LVEF, left ventricular ejection fraction.

The Supplementary online figure is linked to the online version of Paper II at <http://www.nature.com/ajh>

Statistical methods

Statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) following a prespecified data analysis plan. For all tests, a two-tailed $P < 0.05$ was required for statistical significance. Data are presented as mean \pm standard deviation (SD) for continuous variables and as numbers (%) for categorical variables. Differences in baseline characteristics between groups were assessed by Student's *t*-test or by analysis of variance (ANOVA) for continuous variables and chi-square test for categorical variables. To account for the within-subject correlations, general and mixed-effects linear models were used to compare annual measurements of mean BP and ECG-LVH.

Only endpoints confirmed by the endpoint committee were included in the analyses. Analyses were based on the intention to treat principle⁸¹; all randomized patients were included in their treatment group and followed for endpoints for the duration of the study, regardless of protocol violations or adherence to study medication. Patients with multiple endpoints were counted as having had an event in all relevant endpoint analyses; however, only the first event in a specific category was counted in individual analyses.

Cox proportional hazard regression models^{83;106} were used to examine possible associations between time-varying ECG-LVH and the risk of cardiovascular death, MI and/or stroke in ISH patients (Paper I); possible associations between time-varying ECG-LVH and risk of new-onset HF and all-cause mortality in ISH patients (Paper II); and possible associations between baseline and time-varying PP and risk of new-onset AF in patients with hypertension and ECG-LVH (Paper III). Results were reported as HRs with 95% CI. Initially, univariate analyses were performed using the predictor variable in question and other potential risk factors (baseline clinical, demographic and laboratory data). Multivariate analyses were then performed to identify predictors independently associated with the endpoints, adjusted for baseline Framingham Risk Score and a treatment group indicator, and time-varying systolic and/or diastolic BP as prespecified covariates. Additional covariates were selected based on being established risk factors or near significant univariate predictors ($P < 0.10$), which continued to be significant ($P < 0.05$) in stepwise forward and backward regression analyses. Interaction analyses were performed in order to test if the effect of regression of ECG-LVH was stronger in ISH than in non-ISH patients (Paper I and II), and if there were interactions between BP components and other risk factors for new-onset AF (Paper III). Atrial fibrillation event rates over time were illustrated by an unadjusted Kaplan-Meier curve (Paper III).

Summary of the results

Paper I

Electrocardiographic LVH and risk of cardiovascular morbidity and mortality in patients with ISH

The predictive value of regression of ECG-LVH during antihypertensive therapy was investigated in 1320 patients (60.2% women) with ISH and ECG-LVH in the LIFE study. Mean BP at baseline was 174/83 mm Hg and 33.3% had previously untreated hypertension. The composite endpoint of cardiovascular death, non-fatal MI or non-fatal stroke occurred in 179 (13.6%) patients during mean 4.8 years of follow-up. Fatal/non-fatal stroke, fatal/non-fatal MI and cardiovascular death occurred in 88 (6.7%), 67 (5.1%) and 79 (6.0%) patients. In Cox regression models controlling for treatment with losartan or atenolol, Framingham Risk Score and baseline and in-treatment SBP and DBP, regression of ECG-LVH by Cornell product and Sokolow-Lyon voltage were significantly associated with 17% (95% CI: 8-25%) and 25% (95% CI: 13-35%) risk reductions for the composite endpoint per SD reductions in Cornell product (1050 mm x ms) and Sokolow-Lyon voltage (10.5 mm). In parallel analyses evaluating the single endpoints cardiovascular death, fatal and non-fatal MI and fatal and non-fatal stroke; regression of Cornell product and Sokolow-Lyon voltage were significantly associated with lower risks of cardiovascular death and MI; and regression of Sokolow-Lyon voltage with lower risk of stroke. There was a significant interaction ($P=0.048$) between regression of Sokolow-Lyon voltage and lower risk of the composite endpoint of cardiovascular death, non-fatal MI or non-fatal stroke in ISH versus non-ISH patients; ISH patients had an increased outcome effect of regression of Sokolow-Lyon voltage as compared with non-ISH patients.

Paper II

Electrocardiographic LVH and risk of new-onset heart failure and all-cause mortality in patients with ISH

In 9027 patients without a history of HF in the LIFE study, the predictive effects of regression of ECG-LVH for incident HF and the combined endpoint of HF and death were evaluated in 1280 ISH patients and as compared with 7747 non-ISH patients. During mean follow-up of 4.8 ± 0.9 years, new-onset HF and HF or death occurred in 57 (4.5%) and 179 (14.0%) ISH patients and in 220 (2.8%) and 787 (10.2%) non-ISH patients. Cox regression analyses adjusting for treatment with losartan or atenolol and HF risk factors, showed that

regression of time-varying Cornell product was significantly associated with lower risks of new-onset HF and the combined endpoint of new-onset HF and death in patients with ISH and non-ISH. Regression of Sokolow-Lyon voltage was not associated with lower risk of new-onset HF in ISH, neither in crude ($P=0.22$) nor adjusted ($P=0.84$) analyses. However, it was significantly associated with the combined endpoint of new-onset HF and death in ISH, and with both new-onset HF and the combined endpoint in non-ISH. There was a borderline significant interaction for new-onset HF ($P=0.050$) between time-varying Cornell product and ISH status, but not for the combined endpoint of HF and death ($P=0.53$).

Paper III

Pulse pressure and risk of new-onset atrial fibrillation in patients with hypertension and ECG-LVH

We examined whether PP, the pulsatile component of BP and a marker of arterial stiffness, predicted new-onset AF in comparison with other BP components in the LIFE study. In 8810 patients with hypertension and ECG-LVH and neither a history of AF or AF at baseline, Minnesota coding of ECGs confirmed new-onset AF in 353 patients (4.0%) during mean 4.9 years of follow-up. In multivariate Cox regression analyses increase in baseline and in-treatment PP and baseline and in-treatment SBP predicted new-onset AF, independent of baseline age, height, weight and Framingham Risk Score; gender, race and treatment with losartan or atenolol; and in-treatment heart rate and Cornell product. PP was the strongest single BP predictor of new-onset AF determined by the decrease in the -2 Log likelihood statistic (a measure of model agreement with data) in comparison with SBP, DBP and MAP. When evaluated in the same model, the predictive effects of SBP and DBP together were similar to that of PP.

Discussion

Paper I and II

In these LIFE reports regarding patients with ISH *and* ECG-LVH, the results of Cox regression analyses showed significant associations between regression of Cornell voltage-duration product and/or Sokolow-Lyon voltage criteria during antihypertensive therapy and improved cardiovascular outcomes, independent of other risk factors and treatment modality. To our knowledge, this is the first time results of regression of ECG-LVH during antihypertensive treatment have been reported in patients with ISH.

Regression of time-varying Cornell voltage-duration product per 1050 mm x ms (1 SD) was independently and significantly associated with a 17% reduced risk of the primary composite endpoint of cardiovascular death, non-fatal MI and non-fatal stroke; a 25% reduced risk of cardiovascular death and a 17% reduced risk of fatal and non-fatal MI (Paper I); and an 21% reduced risk of new-onset HF and a 17% reduced risk of the combined endpoint of new-onset HF or all-cause death (Paper II). Regression of time-varying Cornell product was not associated with reduced risk of stroke ($P=0.96$) (Paper I). This result deviated from the significant 10% risk reduction for stroke associated with regression of Cornell product in the total LIFE population⁸³ and may represent a type II error due to lack of power (power calculations were based on the primary composite endpoint and not its components). Furthermore, there was a borderline significant interaction ($P=0.050$) between ISH status and time-varying Cornell product for new-onset HF possibly indicating a greater outcome effect of regression of Cornell product in patients with non-ISH (33% risk reduction) as compared with ISH (21% risk reduction) (Paper II). This finding may be subject to a type II error due to low statistical power, and perhaps it should be statistically significant ($P<0.05$). In regard to the combined endpoint of HF or all-cause death, regression of time-varying Cornell product was independently associated with similar significant risk reductions in both subsets of hypertensive patients.

Regression of time-varying Sokolow-Lyon voltage per 10.5 mm (1 SD) was independently and significantly associated with a 25% reduced risk of the composite cardiovascular endpoint; a 28% reduced risk of cardiovascular death; a 23% reduced risk of fatal and non-fatal MI and a 25% reduced risk of fatal and non-fatal stroke (Paper I). Interaction analyses indicated an increased outcome effect of regression of Sokolow-Lyon voltage for the composite cardiovascular endpoint in ISH versus non-ISH patients ($P=0.048$ for

the interaction cross-product). Regression of time-varying Sokolow-Lyon voltage was not associated with reduced risk of new-onset HF in ISH ($P=0.84$), perhaps due to lack of power. It was, however, significantly associated with a 20% reduced risk of the combined endpoint of new-onset HF or all-cause death (Paper II). Furthermore, in patients with non-ISH, time-varying Sokolow-Lyon voltage was significantly associated with a 26% lower risk of new-onset HF and a 20% lower risk of new-onset HF or death per 10.5 mm regression (Paper II).

It is important to note that regression of ECG-LVH was computed per SD reduction in ECG-LVH indices for the *total* LIFE population; i.e. 1050 mm x ms for Cornell voltage-duration product and 10.5 mm for Sokolow-Lyon voltage. This made findings comparable with effect sizes from previous LIFE study reports when plausible; overall the effect sizes of regression of ECG-LVH for most cardiovascular endpoints were quite large (17-28% risk reductions during mean 4.8 years of follow-up) and larger than effect sizes in parallel analyses in the total population⁸³. In our opinion, these effect sizes were of clinical significance.

Our results suggest superior performance for time-varying Sokolow-Lyon voltage compared to Cornell product for prediction of cardiovascular endpoints in patients with ISH compared with non-ISH. A possible explanation for this may be that Sokolow-Lyon voltage LVH is strongly associated with systolic BP and therefore ISH, whereas Cornell product is more related to metabolic risk factors¹⁰⁷. In addition, it may be of importance how the Sokolow-Lyon criteria were originally developed; in the Veteran Administration population of hypertensive patients, a majority of patients had quite severe hypertension with a high contribution of patients with ISH³⁹.

In a study evaluating the prognostic significance of serial ECG voltage in 4,159 patients with ISH enrolled in the Syst-Eur trial⁹³, Fagard et al found a strong association between baseline ECG left ventricular mass defined as the sum of voltages ($R_{aVL}+S_{V1}+R_{V5}$) and new-onset HF, but decrease in the sum of voltages was not a significant predictor of lower HF incidence in multivariate Cox models. Thus, the Syst-Eur findings were consistent with our present finding in LIFE ISH patients; that regression of ECG voltage alone (Sokolow-Lyon criteria) was not associated with lower incidence of HF. Our findings do not exclude that regression of LVH by voltage criteria (e.g. Sokolow-Lyon) is important since the majority of our participants were recruited by having LVH with Cornell product criteria⁸⁰. Furthermore, the interaction analyses showed borderline significance ($p=0.050$) for stronger association between regression of Cornell product and reduced risk of HF in non-ISH than in ISH patients. Combining the Syst-Eur voltage data⁹³, and our Sokolow-Lyon findings in the present study, this finding may overall rank ISH patients somewhat

weaker than non-ISH patients in using ECG-LVH regression to predict incident HF. In variance to the Sokolow-Lyon voltage findings in Syst-Eur and in this study, regression of Cornell product was clinically useful for both new-onset HF and the combined endpoint in both ISH and non-ISH populations. The use of *hospitalization* for new-onset HF to define HF, probably underestimates the true incidence, which again may attenuate the precision of the results.

Our data indicate that the regression of Cornell product may reach a nadir earlier than the regression of Sokolow-Lyon voltage in patients with ISH (Paper I, Figure 2b). In a previous LIFE report, it was indicated that the two ECG-LVH indices recruit different groups of patients¹⁰⁷, and perhaps these groups of patients respond somewhat differently to antihypertensive treatment with respect to regression of ECG-LVH. Overall, these data support the view that both ISH and non-ISH patients should be carefully monitored for regression of ECG-LVH by both Cornell product and Sokolow-Lyon criteria during the treatment of hypertension.

LVH demonstrated by ECG and echocardiography is a strong predictor of cardiovascular disease³⁰ and particularly of cerebrovascular events¹⁰⁸. Previous studies have shown that prevention and regression of both indices of LVH are associated with improved prognosis^{25;26;46;51;83;109}. Echocardiography is preferred in assessing LVH and changes in left ventricular mass owing to low sensitivity of standard voltage criteria (i.e. Sokolow-Lyon voltage) for detecting LVH^{23;39-41;110-115}. However, the use of Cornell voltage-duration product (as an approximation of the true area under the QRS complex) enhances sensitivity of the ECG to ~51%, with a matched specificity of ~95%^{40;41;110;111;114}. The LIFE study was the first prospective study with adequate statistical power to link regression of LVH to reduction of major cardiovascular events; however, this required a large number of patients which was feasible to recruit by ECG and not echocardiography⁷⁹. The presence of Cornell product and/or Sokolow-Lyon voltage criteria, identified hypertensive patients with >70% likelihood of having echocardiographic LVH as well as those not meeting the strict criteria for echocardiographic LVH but with high normal values of indexed left ventricular mass^{116;117}, allowing accurate identification of high-risk status by these ECG indices. Furthermore, regression of Cornell product was associated with greater 1-year reductions in left ventricular mass and a higher likelihood of regression of echocardiographic LVH⁴⁵. Regression of both Cornell product and Sokolow-Lyon voltage were independently associated with reduced risk of major cardiovascular endpoints⁸³ and lower values of indexed left ventricular mass were associated with a 22% reduced risk of the composite

cardiovascular endpoint and 15-35% reduced risks of MI, stroke and cardiovascular death¹⁰⁹. Evaluated together, these ECG and echocardiographic findings indicate that there are strong associations between serial assessments of LVH and cardiovascular outcomes independent of the method used to serially evaluate the degree of LVH. In our opinion, the internal validity was high for the serial ECG assessments used in evaluating cardiovascular outcomes in this LIFE substudy with ISH patients. Unfortunately, we could not evaluate the degree of correlation between serial measurements of electrocardiographic and echocardiographic LVH in ISH as there were very few patients with ISH in the echocardiography substudy ($n=145$, 11% of total ISH population). It is important to note that ECG, albeit having lower sensitivity and positive and negative predictive values, is a less expensive and much more available technique compared with echocardiography¹¹⁶.

Paper III

Increased baseline brachial PP and time-varying PP were independently associated with an increased risk of incident AF independent of other predictors of AF in this population. In comparison with SBP, DBP and MAP as single BP components, PP was the strongest predictor of incident AF based on the decrease in -2 Log likelihood statistic. To our knowledge this is the first study to report a strong, independent association between brachial PP and new-onset AF in patients with hypertension and ECG-LVH.

Both men and women have an approximate 25% overall lifetime risk of developing AF⁵⁹. AF is a cardiac arrhythmia associated with increased risk of cardiovascular morbidity and mortality, and it is, therefore, important to identify modifiable risk factors. These results are in agreement with a Framingham Heart Study report evaluating PP as a predictor for incident AF in a general population with normal or moderately increased BP⁶⁹, which demonstrated that there is a potential weakness of concentrating on SBP alone and ignoring DBP and PP.

Increased PP, a marker of advanced vascular ageing and arterial stiffness^{67;118;119}, may contribute in the structural and electrical remodeling of the myocardium leading to the development of AF, possibly through increased pulsatile load on the heart and increased left atrial size¹²⁰. Studies have shown that reduced distensibility of large arteries parallel cardiac hypertrophy and remodeling in hypertensive patients^{121;122}. Large artery stiffness may increase the work load on the heart similar to volume overload and perhaps represent one of the mechanisms by which hypertension leads to eccentric hypertrophy and left atrial

enlargement¹²². Studies have linked brachial PP to microvascular damage in the heart and other target organs, which again may lead to increased peripheral resistance and MAP, further increasing arterial stiffness and central PP. Increased central PP may then further damage small arteries and lead to LVH¹²³. Brachial PP is a powerful predictor of cardiovascular morbidity and mortality in several studies⁷¹⁻⁷⁸, and its predictive effect increases with age^{74;75;77}. The present study evaluated brachial PP and not central PP. Noninvasive central PP has been shown to better predict cardiovascular outcomes than brachial PP; and to be closer associated with extent of atherosclerosis (carotid plaque burden and intimal-medial thickness, and vascular mass)¹²⁴.

BP was measured with sphygmomanometer, which is considered less accurate than 24-hour ambulatory BP measurement⁷⁴. Analyses of new-onset AF was planned as a secondary endpoint before study termination (September 2001) and unblinding, and not in the 1995 LIFE data analysis plan¹²⁵, however the LIFE study was designed and had statistical power for the primary composite endpoint and the HRs for AF require careful interpretation. Annual ECGs may be more sensitive for detecting sustained AF (i.e. persistent or permanent AF) than for paroxysmal AF. When diagnosing new-onset AF by annual ECGs interpreted at a core laboratory, we most likely missed some instances of paroxysmal AF.

General discussion

This was a substudy of a large multicenter, randomized controlled trial (RCT) in high-risk patients with hypertension and ECG-LVH, in which ISH patients were selected a priori as being of special interest as they are a group of hypertensive patients with especially high risk. Therefore, some possible limitations in the external validity merit discussion. The LIFE ISH patients described here, all had SBP >160 mm Hg and DBP <90 mm Hg, comparable to ISH grade II-III in the current ESH-ESC guidelines¹²⁶. Therefore, it is uncertain whether the results are generalizable to patients with ISH grade I, i.e. SBP >140 mm Hg and DBP <90 mm Hg. Patients included had hypertension *and* ECG-LVH, and the results may not be generalizable to ISH patients without LVH, to patients with systolic-diastolic hypertension without LVH or to normotensives. In this context, it is important to note that the prevalence of ECG-LVH in a Finnish study of 1746 ambulatory patients with hypertension was 9.8% in men and 5.7% in women for Sokolow-Lyon voltage and 14.9% and 18.8%, respectively, for Cornell product

criteria¹²⁷. Patients evaluated in the LIFE study were predominantly white and from countries in Northern Europe and the USA.

In a comprehensive trial like the LIFE study, some statistical considerations should be discussed. Although being a substudy of a comparative antihypertensive trial, in these analyses we adjusted for treatment and did not compare effects of the two treatment regimes. When performing several statistical analyses on the same data, some results, albeit statistically significant, may not be clinically relevant. Moreover, there may be type I errors, i.e. significant test result when the null hypothesis in fact is true. However, our results were consistent in different univariate and multivariate Cox regression models, were in coherence with previous results in the LIFE study, and seemed robust and reliable. Furthermore, it is of great importance to keep in mind that results of regression analyses, demonstrate an association between the dependent and independent variables and does not necessarily imply causality. Also, the analyses of time-varying ECG-LVH and BP during antihypertensive treatment were prespecified and prospective, and adjustment for Framingham Risk Score was selected a priori primarily to account for any difference in key risk factors at baseline. Additional adjustments were based on findings in the univariate analyses (Paper I, II and III), of which some were retrospective of nature (i.e. assessment of baseline predictors of outcomes in the patients included in present analyses). In addition to the main predictor variables, covariates in the multivariate models were selected based on being near significant univariate predictors ($P < 0.10$) which continued to be significant predictors in stepwise forward and backward regression analyses ($P < 0.05$), unless otherwise specified. The total number of covariates in the multivariate models did not exceed 10% of the number of events for the endpoint in question¹²⁸. Furthermore, the phenomenon of regression to the mean may impact the current findings^{83;129}, in regard to the use of values of Cornell product and Sokolow-Lyon voltage above threshold levels to include patients. We attempted to minimize this problem by using separate screening and baseline ECGs^{79;80}. Due to this selection process and the intrinsic variability of ECG measurements¹²⁹⁻¹³², it is likely that both the degree of ECG-LVH at baseline and the subsequent decrease in LVH during therapy were overestimated in some patients. Despite these limitations, improved outcome was associated with lower ECG-LVH, which would actually bias against our findings, as these overestimations due to statistical fluctuations would lead to a more conservative estimate of the impact of ECG-LVH on outcome. Furthermore, assessment of risk based on ECG-LVH criteria considered as time-varying covariates adjusts for both baseline and subsequent levels of these variables, mitigating the impact of any overestimations⁸³. When also taking into account that the sample size and

power calculations for the main LIFE study were based on a 15% reduction in the 5-year event rate of the primary composite endpoint for losartan versus atenolol, it is important to stress that the hazard ratios for the cardiovascular outcomes in these analyses require careful interpretation.

Clinical implications

Our results support the use of Cornell product and Sokolow-Lyon voltage criteria to identify ISH patients who are most likely to benefit from aggressive antihypertensive therapy, and indicate that targeting antihypertensive treatment at regression or prevention of ECG-LVH, and beyond that of lowering BP, may reduce cardiovascular morbidity and mortality in patients with ISH (Paper I and II). This study supports serial measurements of ECG-LVH for risk stratification in patients with ISH undergoing antihypertensive therapy in order to improve their prognosis.

Furthermore, our results support the hypothesis that the relation between BP and incident AF is related specifically to the pulsatile component of BP as assessed by PP⁶⁹, and imply that the association between MAP, i.e. the steady component of BP, and AF, is weak (Paper III). When evaluating risk of AF in hypertensive patients with ECG-LVH, both baseline PP and PP during antihypertensive treatment, alternatively SBP and DBP together, should be considered. Furthermore, lowering of PP may prevent new-onset AF in hypertensive patients with LVH.

Future perspectives

In the past, high BP has been regarded as a normal trait of ageing. It is now evident that hypertension in older individuals, defined by current guidelines^{10;126} is associated with increased risk of cardiovascular outcomes like coronary heart disease, congestive heart failure, stroke, peripheral vascular disease, renal disease and mortality. Hypertension in the elderly is not benign and should be properly diagnosed and treated. More studies are needed to further elucidate the pathophysiology of ISH and increased pulse pressure; to further evaluate if treatment should be targeted at regression of ECG-LVH in patients with ISH, and not only at specific BP values; and to further evaluate if reduced PP prevents incident AF.

Conclusions

Paper I

Regression of ECG-LVH determined by Cornell voltage-duration product and Sokolow-Lyon voltage, were significantly associated with lower risks of cardiovascular morbidity and mortality, independent of treatment modality, baseline Framingham Risk Score and time-varying SBP and DBP in patients with ISH and ECG-LVH. ISH patients had an increased outcome effect of regression of Sokolow-Lyon voltage for the composite endpoint of cardiovascular death, MI and stroke as compared with non-ISH patients.

Paper II

Regression of ECG-LVH determined by Cornell voltage-duration product was associated with similar significant reductions in risk of new-onset HF and the combined endpoint of HF or all-cause mortality in ISH and non-ISH patients, independent of treatment modality, baseline Framingham Risk Score and UACR, history of AF and time-varying SBP.

Paper III

Increased baseline and in-treatment PP were associated with increased risk of new-onset AF in patients with hypertension and ECG-LVH, independent of baseline age, height, weight and Framingham Risk Score; gender, race and treatment modality; and time-varying heart rate and ECG-LVH by Cornell voltage-duration product. As compared with SBP, DBP and MAP, PP was the single BP component with the strongest predictive effect.

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